Remarks

Claims 84-90, 92-101, and 103 are currently under consideration. Applicant respectfully requests reconsideration of the rejections in the office action in view of the remarks set forth below.

Rejections Under 35 USC §103(a)

(1) Claims 84-90, 92-101, and 103 stand rejected under 35 USC §103(a) as being unpatentable over Delgado et al., *J. Bacteriol.*, 183, 4543-4550 (2001) (Delgado), in view of Korzheva et al., *Science*, 289, 619-625 (2000) (Korzheva), Darst et al., U.S. Publication No. 2002/00348008, (Darst) and Woychik and Hampsey, *Cell*, 108, 453-463 (2002) (Woychik). Applicants respectfully traverse this rejection.

The Amino Acid Locations In the Present Application Are Not Those Of Interest In the Cited References

Applicants respectfully disagree with several of the Examiner's assertions in item 9 of the office action, on pages 5-6. The examiner seems to suggest, incorrectly, that a novel element of the instant invention is the observation that MccJ25 targets bacterial RNAP, and that MccJ25 targets the RNAP region spanning amino acids 842-1140. The novelty of the instant invention is the discovery that amino acids 736-747 and 779-781 of the RNAP β′ subunit are a useful target for compounds that block DNA transcription. See the present application, page 10, line 5.

This contrasts starkly with the mutation discovered by Delgado in residue 931 of the RNAP β′ subunit, that changing threonine to isoleucine confers resistance to MccJ25. Obviously, residue 931 is at an entirely different location on the RNAP β′ subunit from the amino acids of interest in the instant invention at locations 736-747 and 779-781 of the RNAP β′ subunit.

The distinct locations of the modifications to the RNAP β′ subunit is patentably significant. It should be apparent to a skilled person in the field of molecular biology that different mutations and different locations on a protein or DNA segment have different functions. For example Woychik, on page 455, right column, bottom paragraph, discusses site-

specific DNA cross-linking experiments to define the contact points of TFIIF, a subunit of RNAP, with template DNA. Furthermore, Korzheva discusses cross-links at specific locations of the "β' C Rudder," at amino acides 298-330, 321, and 325. Korzheva, page 622, right column, center. From this discussion, it should be clear that this protein (or any protein) is not a monolithic entity where a change at one position is equivalent to a change at another position. Accordingly, the examiners assertion in item 9, page 6, lines 6-8 that an agent that binds to the RNAP β' subunit "would necessarily bind to any amino acid of RNAP β' subunit" is logically incorrect and scientifically inaccurate.

Still further, the reference to Korzheva in item 9 appears to be based on a misunderstanding of the subject matter of the invention. The examiner states: "Korzheva et al teach that the secondary channel is responsible for the diffusion of incoming nucleotide substrate into the active site of the RNAP (see abstract and Figure 3), to overcome access to the main channel which is blocked by the nucleic acid framework." This remark suggests the examiner believes the present Applicants are seeking to claim the RNAP β' subunit secondary channel per se. That is incorrect. The present Applicants have identified a specific region of interest in the secondary channel only, and specifically enumerated residues, that are clearly stated in the currently amended claims. The subunit that we are claiming is not discussed in any of the cited references. The teachings of Korzheva, and the other references cited by the examiner, would not lead a person skilled in the art to focus on the regions that the instant inventors have focused on. Further, the functions cited by the examiner in Korzheva (diffusion of incoming nucleotides) is not part of the subregions of this invention.

Thus, neither Delgado nor Korzheva, while publications in related subject matter, do not read on any specific aspect of the instant invention and are not proper references, alone or in combination.

The "Wherein" Distinguishes The Present Application From the Cited Art

The examiner suggests in item 9 on page 6 that the "wherein" clause, in amended claim 84, does not carry patentable weight. Applicants respectfully traverse this assertion. The "wherein" clause in claim 84 serves to distinguish the present invention from Delgado, by

explicitly limiting the amino acids of use in the present method to 736-747, and 779-781 of the β′ subunit of RNAP. As noted above, Delgado was concerned with a mutation at amino acid 931 of the RNAP β′ subunit.

Applicant respectfully directs the Examiners attention to MPEP 2106(II)(C) and 2111.04 for a discussion of claim language that may have a limiting effect on claim, including "wherein" clauses. It should be clear from the amended claim 84 of the instant application that the wherein clause here does not "suggest or make optional" the limitations on the alignment of the RNAP homologous secondary channel to residues 736-747 and 779-781. The instant wherein clause is a firm claim limitation.

The determination of whether a clause, such as a "wherein" clause, is a limitation in a claim depends on the specific facts of the case. MPEP 2111.04. In some cases, for example, a clause such as a "wherein" or "whereby" clause can be used to express an intended result in a process step. In such usage, the limiting clause should not be given patentable weight. *Id.*, citing to *Hoffer v. Microsoft*, 405 F.3d 1326, 1329 74 USPQ2d 1481, 1483 (Fed. Cir. 2005). That is not the case here. In this present case, claim 84 is limited to sequences corresponding to, and alignable with, amino acid residues 736-747 and 779-781. This is not a suggested or optional limitation. It is a firm limitation that clearly places the sequences of interest outside the scope of residue 931 studied by Delgado.

Conclusion Related to Examiner's Item 9

In view of the remarks above noting that the residues of interest in the present case are outside the scope of the specific residues in the cited reference, and that the difference in scope is scientifically significant, and that the wherein clause deserves patentable weight to further distinguish the instant claims from the cited art, applicants believe they have overcome the rejection under 35 USC §103(a) maintained at the end of item 9. Accordingly, Applicants respectfully request that the examiner withdraw this rejection.

Additional Obviousness Rejections – Item 13

In item 13, the Examiner raises another obviousness rejection, that it would have been obvious to one of ordinary skill to use the method (from Darst) of identifying an agent that binds to a specific domain of prokaryotic RNAP with a eukaryotic RNAP for "the known and expected result of providing a means recognized in the art to identify the basis of differential specificity within species and how that specificity contributes to sensitivity towards agents capable of inhibiting RNA synthesis activity." Applicants respectfully traverse the assertion that the above argument is obvious or relevant to the instant invention.

This argument fails to intersect with the invention under examination, because the Applicants have identified a specific location of the RNAP β′ subunit that are nearly invariant among bacterial RNAP, but are significantly different from eukaryotic RNAP. Page 10, lines 9-11. Applicants found compounds that bind to the identified regions, and are believed to be useful to block transcription. *Id.* This invariant region is not disclosed in any of the cited art. Furthermore, the inventors have discovered that blocking the RNAP secondary channel with a small molecule prevents uptake of NTPs by RNAP and therefore inhibits transcription. Page 9, line 30-page 10, line 2. This is not a "means recognized in the art to identify the basis of differential specificity within species and how that specificity contributes to sensitivity towards agents capable of inhibiting RNA synthesis activity." There is no such means recognized in the art.

Further, Applicants respectfully assert that there is "means recognized in the art for identifying differential specificity within species." Any attempt to identify differential specificity must rely on experimentation and innovation. In the instant case, the means used to identify the target regions of interest is disclosed in the experimental procedures in Example 1, on pages 60-66 of the present application. The results are summarized in Tables 1 and 2 on pages 50-52.

The Woychik and Korzheva references are not directed to the inhibition of RNAP mediated transcription. Darst discloses a method for identifying agents that inhibit RNAP activity, but there is no suggestion in Darst to combine his method with the sequence locations identified in the instant application. Therefore, a skilled person would not have any motivation

to look to amino acid residues 736-747 and 779-781 for use in identifying inhibitory compounds. Furthermore, there is no motivation to combine the cited references to arrive at the instant invention.

Still further, Darst teaches away from any distinction between bacterial and eukaryotic RNAP with the assertion in paragraph 181 that there is a high degree of sequence homology between prokaryotes and eukaryotes.

Accordingly, applicants respectfully request that the examiner withdraw the obviousness rejection stated in item 13 of the office action.

Rejection In Item 15

The rejection in item 15 of the office action rests on many of the same arguments as were addressed in item 9, with the additional element of the "obvious to try" test, as discussed by the Supreme Court in *KSR v. Teleflex,* 550 US __, 127 S.Ct. 1727, (2007). The Examiner suggests that the problem being solved was trying to understand the mechanism of antibiotic MccJ25. In reality, the instant invention is directed to a method of identifying new antibiotics. Still further, merely because Delgado identified a mutation at residue 931, that does not in any way suggest the residues identified in the current work. This is not a "finite, predictable solution" as stated in the *KSR* decision. The β′ subunit of bacterial RNAP has at least 1500 amino acid residues (Darst, Fig. 1). Further, even though it was known that MccJ25 targets the β′ subunit of RNAP, substantial experimentation would be required to find other relevant target residues. The Examiner further states that because yeast RNAP II shares a high level of homology with human RNAP, that a skilled person would be motivated to examine those residues (presumably in common). However, it is not stated in the office action, and not clear to the Applicants, which specific sequences the Examiner is referring to. In fact, the method used by the present inventor to identify the sequences of interest in the instant invention are discussed in Example 1, at pages 49-55, and tables 1-4 on the same pages.

The intent of the TSM test, in *KSR*, was to question applications based on familiar elements according to known methods that are likely to yield predictable results. *KSR*, slip op. at 12, see also MPEP 2141. However, Applicants assert here that the "elements" of the β′ subunit

of bacterial RNAP are not familiar, but rather require extensive analysis and experimentation to harness their utility. The identification of the binding sites by the present inventor that are valuable to identify new antibiotics are not the result of ordinary and skill and common sense, but rather extensive experimentation and innovation. This is hardly a rearrangement of old elements, nor a predictable use of prior art elements according to their established functions. *Id.*, at 13.

Finally, there is a tremendous need to identify new antibiotics in the state of the art. See, for example, Darst at paragraphs 7-9 for a general discussion. The ravages of bacterial infections are not diminishing. This is an important secondary factor suggesting that innovation, as here, in identifying new antibiotics is an important and worthy need. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Conclusion Regarding Obviousness Rejections

For the reasons set forth above, Applicants believe they have responded to each obviousness rejection in the office action. Accordingly, Applicants respectfully request that the rejections be withdrawn.

Rejection Based on 35 USC §112, First Paragraph

Claims 86-89, 95, and 97-99 stand rejected under 35 USC §112 first paragraph, as allegedly failing to comply with the written description requirement. See office action, page 11, item 17. Applicants respectfully traverse this rejection.

The claims listed in this rejection all enumerate ranges of amino acid residues with at least one substitution, insertion, or deletion of an amino acid residue with the stated ranges. The Examiner alleges, on page 13 item 21, that the claimed "bacterial RNAP homologous secondary channel amino acid sequence having at least one substitution, insertion, or deletion of amino acid residues" is generic and not supported in the specification. Applicants respectfully disagree with this assertion.

Claims 86-89, 95, and 97-99 are based on the disclosure in the specification on page 14 line 23 to page 15 line 9. A substantial series of actual and specific β' subunits with amino acid

substitutions and deletions are disclosed in Example 1. See the discussion starting on page 49, line 28 describing how the β′ subunits were prepared and isolated. Table 2 on pages 51-52 and Table 5 on pages 56-57 of the specification list the isolates with the amino substitution on each isolate. One deletion is listed, in Table 5 at amino acid 735, where alanine was deleted, as marked by a "Δ" symbol.

Contrary to the Examiners allegation at the end of paragraph 21, Applicants respectfully assert that the above explanation and the data in Tables 2 and 5 make clear that the examples of the invention are clearly defined and described.

Additionally, in item 22 on pages 13-14 of the office action, the Examiner alleges that the rejected claims "lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples." Presumably, the Examiner is referring here to the data of amino acid substitutions and deletions presented in Tables 2 and 5. The correlation between function and structure is disclosed in the discussion around these tables, by the indication of "MBC," or mean bactericidal concentration. For example on page 52 of the specification the inventor notes that the substitutions disclosed in Table 2 map to various physical locations of the RNAP secondary channel (lines 19-25).

With respect to the Examiner specific statements in item 22, the modified peptides of claims 86-89, 95, and 97-99 are described in the specification by functionally and structurally, with a correlation therebetween. The correlation between structure, i.e., substitution or deletion of amino acid residues as claimed, and bactericidal activity is clearly set forth in Tables 2 and 5. The purpose of preparing the mutations is to probe the activity of the RNAP secondary channel. See page 49, line 23-31. Accordingly, applicants respectfully assert that there is ample written description supporting the claims.

In item 23 of the office action, the examiner seems to suggest that the examples do not support the scope of the alleged genericness of the claims, and the examiner used a calculation (center, page 15) to support that contention. The examiners assertion implying that the claims may not exceed the four corners of the examples is legally incorrect. MPEP 2163(II)(A)(3)(a)(ii) (page 182 in the MPEP); see also *Enzo Biochem, Inc. v. Gen-Probe Inc.* 323 F.3d 956, 966-968 (Fed. Cir. 2004). The written description requirement for a claimed genus may be satisfied

through sufficient description of a representative number of species by actual reduction to practice. *Id.* Here, Tables 2 and 5 show a substantial number of actual substitutions and one deletion to support the claimed invention. Accordingly, Applicants believe the suggestion that Tables 2 and 5 do not support the alleged lack of written description is erroneous.

Rejection Based on 35 USC §112, Second Paragraph

In item 29, the Examiner asserts that the references to *Bacillus subtilis* in claim 86 lack antecedent basis, because there is no reference to *Bacillus subtilis* in the base claim. Applicants respectfully traverse this rejection.

The reference to *Bacillus subtilis* in claim 86 is not dependent on claim 84, the base claim. The reference to claim 84 is only to the "first entity" in claim 84. Claim 86 provides the additional limitation that the first entity from claim 84 is selected from *E. coli* or *B. subtilis*, and includes additional detail on substitutions, insertions, or deletions at the enumerated ranges of RNAP of those two bacteria. The use of the grammar article "a" preceding *E. coli* or *B. subtilis* RNAP on the second line of claim 86 signals that this is the first reference to these items, and that the reference to *E. coli* or *B. subtilis* in claim 86 is not dependent on the base claim. Accordingly, antecedent basis for the references to *Bacillus subtilis* in claim 86 is not required.

In item 30, the Examiner makes a similar rejection, of the reference to *Bacillus subtilis* in claim 89, which is dependent on claim 87. Again, the reference to claim 87 is only to the "second entity" in claim 87. Claim 89 provides the additional limitation that the second entity is selected from *E. coli* or *B. subtilis*, and includes additional detail on substitutions, insertions, or deletions at the enumerated ranges of RNAP of those two bacteria. The use of the grammar article "a" preceding *E. coli* or *B. subtilis* RNAP on the second line of claim 89 signals that this is the first reference to these items, and that the reference to *E. coli* or *B. subtilis* in claim 89 is not dependent on the base claim. Accordingly, antecedent basis for the references to *Bacillus subtilis* in claim 89 is not required.

Virtually identical arguments are repeated in items 31 and 32 of the office action. A repetition of the Applicants response will not be repeated as needlessly repetitive, but Applicants

respectfully assert that the rejections in items 31 and 32 are erroneous for the reasons provided in the preceding two paragraphs.

Item 33 is an additional rejection under §112 second paragraph, that "derivatives of *E. coli* RNAP or *B. subtilis* RNAP" is unclear in claims 86, 89, 95, and 99. Applicants respectfully traverse this rejection. It should be clear that Applicants are claiming modified forms of bacterial RNAP in this aspect of the invention. In claims 86, 89, 95, and 99, the *E. coli* RNAP and *B. subtilis* RNAP are specified as having amino acid insertions, deletions, or substitutions. This is disclosed in the specification on page 14, line 23 to page 15, line 9, and in the data in Tables 2 and 5 of the specification, on pages 51-57 of the specification. Accordingly, Applicants believe that the claimed subject matter has sufficient specificity to meet the requirements of §112, second paragraph.

Nonstatutory Obviousness Type Double Patenting Rejection

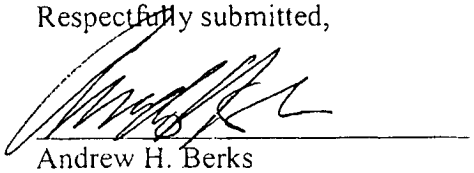
Claims 94-90, 92-101, and 103 are provisionally rejected on the ground of nonstatutory obviousness type double patenting over claims 8-12 and 17-25 of co-pending application 10/571226. Applicants respectfully traverse this rejection.

A nonstatutory obviousness type double patenting is appropriate where a conflicting claim is either anticipated by, or would have been obvious over, the reference claims. See MPEP 804(II)(B)(1) and references cited therein. In the present case, the cited reference does not anticipate or render obvious the instant claims, because the cited reference is not available as art under §102 or §103, since the instant application was filed earlier in time than the cited reference. The instant application is based on PCT/US03/27547, with international filing date September 4, 2003. The cited reference is based on PCT/US04/28640, with international filing date September 2, 2004. Accordingly, since the instant application was filed earlier in time than the cited reference, co-pending application 10/571226 is not available as a reference that can be cited against the instant application. Accordingly, Applicants request that the rejection be withdrawn.

Conclusions

Applicant believes that all rejections are fully responded to, and that the instant claims are in condition for allowance. Favorable action on the same is earnestly solicited. If the Examiner has any questions, she is invited to contact the undersigned at the telephone number below.

Respectfully submitted,



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